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09/161,680    09/28/98    BORNSCHEUER

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EXAMINER

KERR, K

ART UNIT

PAPER NUMBER

1652

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

# Office Action Summary

Application No.  
**09/161,680**

Applicant(s)

**Bornscheuer et al.**

Examiner

**Kathleen Kerr**

Group Art Unit

**1652**

☒ Responsive to communication(s) filed on 6/26/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

☒ Claim(s) 1, 2, and 4-9 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1, 2, and 4-9 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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## DETAILED ACTION

### *Application Status*

1. The amendment-after-final, filed on June 29, 2000, has been entered amending claims 6 and 7 of the pending claims 1, 2 and 4-9. The Examiner has reopened prosecution of the instant application, after-final, based on a reconsideration of the claims. Thus, the instant Office action is non-final. Claims 1, 2, and 4-9 are pending in the instant Office action.

### *Information Disclosure Statement*

2. The Winnacker reference and the Harpes reference have now been considered as noted in the updated, attached copy of the information disclosure statement. Additionally, applicants should note the corrections in the citations made by the Examiner.

### *Previous Objections/Rejections to the Claims now Withdrawn*

3. As applicants correctly noted in their response, Paper No. 11, the previous objection of Claim 5 was a typographical error. The correct objection was of Claim 6 for the reasons cited in the previous Office action. That objection is withdrawn by virtue of applicants amendment to Claim 6.

4. The previous rejection of claims 6 and 7 under 35 U.S.C. 112, second paragraph, is withdrawn by virtue of applicants amendment to said claims.

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*Previous Rejections Maintained*

5. The rejection of claims 1-2 and 4-8 under 35 U.S.C. 102(b) as being anticipated by Greener et al. is maintained by the Examiner. See *Response to Arguments* below.
6. The rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Greener et al. in view of Wilks et al. is maintained by the Examiner. See *Response to Arguments* below.

*New Objections to the Claims*

7. Claim 1 is objected to for the following informality:
  - a. In line 7, the word "From" is inappropriately capitalized.Appropriate correction is required.
8. Claims 4, 8, and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 4 does not further limit the subject matter of its parent claim, claim 1, because claim 4 limits the bacteria, which are in a Markush group, to either Gram-positive or Gram-negative bacteria. This limitation does not exclude any bacteria, and, thus, does not further limit the parent

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claim. Applicants have not limited the microorganism to Gram-positive or Gram-negative bacteria; this limitation would appropriately limit the dependent claim 4.

Claim 8 does not further limit the subject matter of its parent claim, claim 1, because all enzymatic activity is "selective" according to the commonly held definition of enzymatic activity in the art of enzymology. Thus limiting the alteration step to the production of a selective enzyme does not materially limit the subject matter of the parent claim.

Claim 9 does not further limit the subject matter of its parent claim, claim 8, because the terms regio-, chemo-, and stereoselective encompass all enzymatic activity thus not materially limiting the subject matter of the parent claim.

#### *New Claim Rejections - 35 U.S.C. § 112*

The quotation of the second paragraph of the statute can be found in Paper No. 7.

9. Claim 1, and dependent claims 2 and 4-9, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In section 1(c), the definition of the term "impeding activity" is unclear whether it refers to the mutating activity, the new enzyme's activity, or some other activity. Also, in section 1(d), the claim language is cumbersome and confusing. Applicants must rewrite this section to clarify exactly what constitutes the method step that is being claimed.

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10. Claim 8, and dependent claim 9, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "selective" in claim 8, line 3, is a relative term which renders the claim indefinite. The term "selective" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 1, and dependent claims 2 and 4-9, are rejected under 35 U.S.C. 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the methods of the invention. The instant claims are drawn to methods of altering substrate specificity of an enzyme. Applicants have failed to enable the duplication of their own experiments using the plasmid 2792.1 that contains the *estF* gene which encodes PFE, a term which the Examiner can only assume denotes an esterase enzyme since PFE is only defined as the gene product of *estF* in the instant specification. Applicants have also failed

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to enable the broader applications of the methods of the instant claims. The requirement of undue experimentation will be addressed for both these inadequacies in the enablement of the application.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

In the first case, applicants have failed to enable the duplication of the experiments included in the instant specification. While applicants give detailed instruction of the practice of

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their methods using a particular example, one of skill in the art would be required to obtain applicants' plasmid, 2792.1, which is an integral part of the example. Applicants have not deposited said materials nor have they described said materials in such a way as to be duplicated by a skilled artisan. Particularly striking is the fact that the gene, *estF*, in applicants' example is undefined in the instant specification and cannot be identified in GenBank, a common depository for DNA sequences encoding enzymes. Furthermore, the gene product, PFE, remains undefined. It would thus be impossible for one of skill in the art to duplicate applicants' method as exemplified in the instant specification.

In the second case, applicants have failed to enable the broader applications of the methods of the instant claims. The instant claims are broadly drawn to methods which create enzymes having altered substrate specificity using a strain of bacteria, *Escherichia coli* strain XL1 Red, which strain randomly introduces mutations into DNA and which is commercially available and commonly used by skilled artisans to produce random mutations. While applicants include a single, effective example of the instant methods, the ability to alter an enzyme's substrate specificity by *random* mutation, without any selective pressure on the mutagenesis, is wholly and entirely unpredictable as indicated by the word *RANDOM*. Applicants' methods, while requiring a selective medium, do not indicate how a particular compound (i.e., enzyme substrate) in the growth medium of the mutating bacteria directs the random mutagenesis to particularly and predictably alter the enzyme's substrate specificity. This lack of predictability is especially poignant when considering that the linear DNA sequence of the average encoded protein contains



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no structural relationship to the particular positions of the encoded residues involved in the substrate specificity of the enzyme. Thus, it would be impossible to predictably direct random mutagenesis on DNA to particularly alter an encoded enzyme's substrate specificity.

### *Response to Arguments*

12. In reply to the Examiner's rejection of claims 1-2 and 4-8 under 35 U.S.C. 102(b) as being anticipated by Greener et al., applicants argue that Greener et al. do not inherently practice the method steps of the instant claims because Greener et al. contain no evidence whatever of any alteration in substrate specificity of the enzyme. The Examiner disagrees. The alteration in specific activity would inherently be recognized as an alteration in substrate specificity by one of skill in the art since the commonly held definition of substrate specificity in the art is directly correlated with enzymatic (specific) activity wherein  $\text{substrate specificity} = k_{\text{cat}}/K_m$  and  $k_{\text{cat}} = \text{enzymatic (specific) activity}$ . Thus, the inherent matter *is* necessarily present in the prior art reference and an ordinarily skilled artisan would recognize this fact.

13. In reply to the Examiner's rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Greener et al. in view of Wilks et al., applicants argue as described above and thus the combination of Greener et al. and Wilks et al. would not obviate claim 9. The Examiner disagrees for the reasons cited above.

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*Summary of Pending Objections/Rejections*

14. The following rejections are maintained from previous prosecution:
  - a. Claims 1-2 and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Greener et al.
  - b. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Greener et al. in view of Wilks et al.
  
15. The following objections/rejections are newly presented in the instant Office action, thus necessitating non-final status:
  - a. Claim 1 is objected to for an informality.
  - b. Claims 4, 8, and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a parent claim.
  - c. Claim 1, and dependent claims 2 and 4-9, are rejected under 35 U.S.C. 112, second paragraph, because of the indefinite term "impeding activity" in Claim 1(c) and because of the cumbersome and confusing language in Claim 1(d).
  - d. Claim 8, and dependent claim 9, are rejected under 35 U.S.C. 112, second paragraph, because of the relative term "selective" in Claim 8.
  - e. Claim 1, and dependent claims 2 and 4-9, are rejected under 35 U.S.C. 112, first paragraph, enablement.

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*Conclusion*

No claims are allowed in the instant application for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Kathleen M. Kerr whose telephone number is (703) 305-1229. The Examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



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July 10, 2000